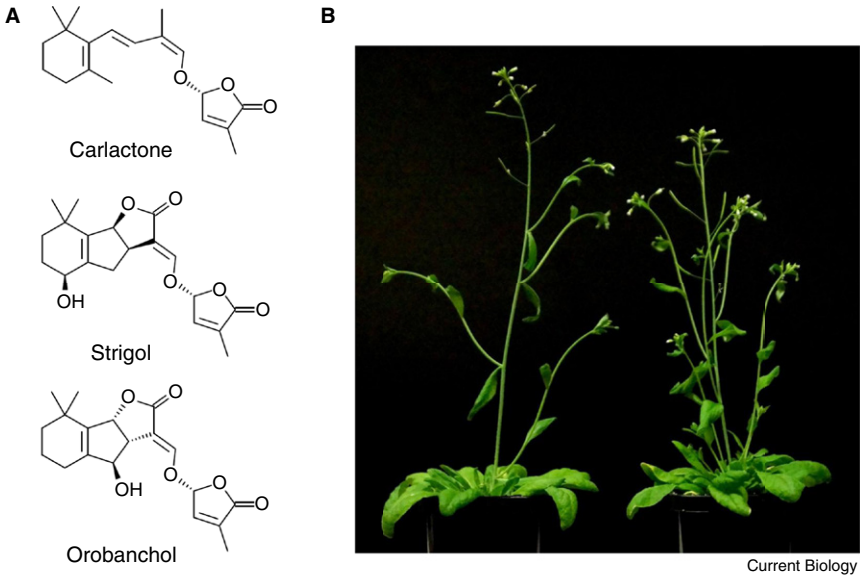

Figure 1. Strigolactones.
Chemical structures of the strigolactone intermediate, carlactone, and representatives, strigol and orobanchol, of the two main classes of strigolactone. Where present, the four rings shown are designated ABCD, named sequentially from left to right (naming not shown). (B) *Arabidopsis* wild-type (left) and *max4* strigolactone deficient mutant (right).

shoot branching is inhibited by strigolactone. Dependent on phosphate and carbon status, strigolactones supress root growth and adventitious rooting and enhance root hairs and nodulation. In the shoot, in addition to branching inhibition, they affect stem elongation (plant height) and secondary growth (wood production).

How do they work? Major components of the perception and signalling pathway have already been revealed. These include an α/β hydrolase as receptor and a complex of players including a DELLA protein and an F-Box protein. In shoots, a protein named D53 has been shown to be targeted for degradation in the presence of strigolactones and this degradation is required for branch inhibition. The downstream targets are not yet proven, but are likely to differ for different processes.

Strigolactone deficiency is often associated with enhanced auxin transport. For shoots, there is ongoing debate about relative roles of auxin transport and the direct action of strigolactones on other pathways such as through Teosinte Branched-1 (TB1; other names BRC1 and FC1). An enhancer of TB1 gene expression was identified as the main cause of decreased tillering and enhanced yield in domesticated maize compared with its wild progenitor, *teosinte*.

Do they have commercial potential? Yes, based on all the effects of strigolactone many commercial opportunities could arise — wood production, shoot architecture, adventitious rooting, root development, nutrient acquisition, parasitic weeds and more. Already it is possible to identify certain strigolactones that affect one process and not another. However, one challenge is to identify stable strigolactones or methods of delivery that enhance stability. The opportunities for genetic manipulation of the pathway are also clear.

Where can I find out more?

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School of Biological Sciences,
The University of Queensland, St. Lucia,
Brisbane, 4072, Australia.
E-mail: c.beveridge@uq.edu.au

Primer

Adipocytes

Rana K. Gupta

In the United States alone, one-third of adults and nearly one-quarter of children are clinically obese. This growing epidemic is of serious concern as obesity confers a significant risk to developing numerous chronic conditions, including cancer, diabetes, and heart disease. The alarming incidence of obesity and the rising costs of treating the associated diseases has increased the urgency of acquiring a deeper understanding of all aspects of adipocyte (fat cell) biology, including how these cells form, how they are regulated, and how increased adiposity leads to disease. Since the turn of the new century we have witnessed great progress in understanding the complexities of adipocyte function and their developmental origin. As a result, our view of adipocytes has now changed dramatically. Here, I provide a brief primer on some of the hot topics that have emerged in this field of research, which now includes aspects of endocrinology, cardiology, cancer biology, and stem cell and developmental biology. I also highlight some of the unique opportunities for therapeutic targeting of adipose tissue in metabolic disease.

The many functions of adipocytes

Storage and release of excess energy

In vertebrates, many cell types can accumulate lipid; however, the evolution of specialized fat-storing cells ('white adipocytes') has provided a safe and specific compartment for this purpose. White adipocytes are characterized by the presence of a single large lipid droplet and are therefore also known as 'unilocular' adipocytes. Their classical function, first and foremost, is to serve as an energy bank (Figure 1). During times of energy excess, free fatty acids (FFAs) enter adipocytes following the hydrolysis of triglycerides from triglyceride-rich lipoproteins and chylomicrons. FFAs are then re-esterified into triglycerides through the sequential actions of multiple enzymes, including glycerol-3-phosphate acyltransferase

(GPAT), 1-acylglycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP), and diacylglycerol acyltransferase (DGAT). Adipocytes can also synthesize lipid from carbohydrates through *de novo* lipogenesis. When energy levels are low, adipocytes contain the enzymatic machinery — comprising adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL) — required to hydrolyze triglycerides and release FFAs back into circulation.

Lipid trafficking in adipocytes has been extensively studied for the past decade; however, there remains much to learn. The principle enzymes in adipocyte triglyceride metabolism have been identified, although the precise function and relative importance of these enzymes and their distinct isoforms *in vivo* remain unclear. A better understanding of how these mechanisms are utilized in human adipose tissue, and how they are dysregulated in metabolic disease, will also be essential. More recently, it has become clearer that proteins associated with the lipid droplet, such as the perilipin family of proteins, play an important role in regulating lipolysis and lipid metabolism in adipocytes. Understanding the precise functions of these various proteins and how they communicate with other pathways within the cell is of great interest. Furthermore, lipid intermediates themselves can serve as signaling molecules in adipocytes, through binding to nuclear hormone receptors or interacting with second-messenger systems. Identifying and characterizing these various lipid signals is an ongoing challenge in the field.

Endocrine role

For nearly a century, adipocytes were appreciated solely for their energy storage capacity. This view began to change with the discovery that adipose tissue in obesity produced tumor necrosis factor α (TNF-α), a pro-inflammatory cytokine that drives insulin resistance; this provided the first link between adipose-secretory products and insulin resistance in obesity. The discovery of the hormone leptin was a pivotal point in the field of energy metabolism. Leptin is produced and secreted by adipocytes and functions centrally to regulate satiety. Leptin also acts on peripheral tissues to control nutrient homeostasis and inflammation. Importantly, this discovery provided evidence of a now widely appreciated endocrine role for adipocytes. Contemporaneously, two other 'adipokines' (adipocyte-derived cytokines) — adiponectin and adipsin — were identified. Adiponectin is produced almost exclusively by adipocytes and exerts powerful and pleiotropic effects on glucose and lipid metabolism, and also provides cardioprotection. Adipsin, also expressed exclusively in adipocytes, acts in an adipose–pancreas inter-organ axis to regulate the insulin-secretory capacity of β-cells.

The list of adipokines is growing and their widespread effects on energy balance, cardiovascular function, immune regulation, and nutrient homeostasis are becoming more and more evident. There is tremendous excitement and promise in understanding the wide range of physiological roles for these adipose secretory proteins because many adipokines exhibit therapeutic potential. However, the complexity of their action also represents a challenge for the design of effective and specific treatments. Going forward, the specific mechanisms by which adiponectin, leptin, and other adipokines elicit their functions in different target tissues will need to be further elucidated. Moreover, the relative importance of many of these factors remains unclear. Targeted deletions of cognate receptors or target pathways in animal models will ultimately help provide insight into the precise roles of many of these adipokines.

Thermogenic adipocytes: brown and beige

In addition to the energy-storing white adipocytes described above, all mammals have a second major type of adipocyte that functions to convert chemical energy into heat. These thermogenic 'brown adipocytes' are characterized by their abundance of mitochondria (which give the cells their brown appearance) and multilocular fat droplet appearance (Figure 1). Distinct depots of brown adipose tissue (BAT) are most abundant in the interscapular region of small mammals and infants, and develop during embryonic development. Brown adipocytes likely evolved to help defend animals against the cold and were historically referred to as the 'hibernating organ' due to their function in maintaining body temperature in hibernating animals and newborns.

Brown-like adipocytes also appear within distinct white adipose depots as dispersed pockets of multilocular cells. These cells, now termed 'beige adipocytes', represent recruitable thermogenic cells that arise in response to cold challenge, exercise, and under pathological conditions such as cancer-associated cachexia. Beige fat cells play a meaningful role in the regulation of glucose homeostasis and energy balance. These cells, although thermogenic, appear to be molecularly and developmentally distinct from brown adipocytes that form during development (often termed 'classical BAT'). Adult humans contain appreciable amounts of active thermogenic adipose tissue; molecular analyses suggest that this tissue closely resembles the rodent beige fat, but also has some features of classical brown adipocytes.

The thermogenic function of brown and beige adipocytes is mediated by the specific expression of uncoupling protein 1 (UCP1). UCP1 is a transport protein that sits within the inner membrane of mitochondria and catalyzes a proton leak across the inner membrane, dissipating the electrochemical gradient that has been generated via the electron transport chain, thereby uncoupling oxidative metabolism from ATP synthesis. Heat production occurs as the biochemical reactions involved in mitochondrial fuel oxidation are subsequently accelerated. Tremendous effort is focused towards identifying 'druggable' regulators of UCP1 expression or activity.

In rodents, BAT is densely innervated; the thermogenic program is critically regulated by β-adrenergic signaling in brown adipocytes. The story of beige adipocyte activation in subcutaneous white adipose tissue (WAT) has become more interesting and complex. In response to the cold, beige adipocytes arise mostly through *de novo* fat cell differentiation, rather than through a direct conversion of mature white adipocytes into UCP1$^+$ cells. Local catecholamine production occurs in alternative macrophages within WAT, activated by eosinophil-derived interleukin-4 (IL-4). This immune cell cascade appears critical for cold-induced beige cell

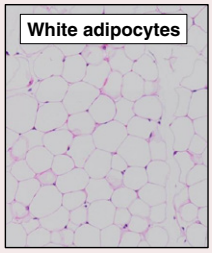
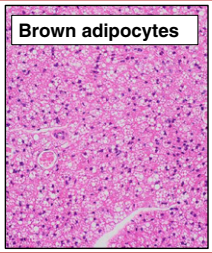
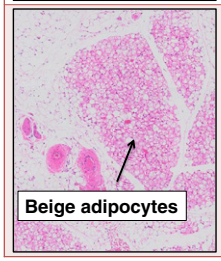
Adipocytes	Appearance	Function	Location in rodents	Location in humans	Developmental origin
 White adipocytes	'Unilocular' fat droplet	Lipid storage Production of endocrine hormones regulating nutrient homeostasis, food intake, cardiovascular function, and inflammation Tissue regeneration	Widespread: organized into anatomically distinct depots	Widespread: organized into anatomically distinct depots	Varies from depot to depot, and potentially within depots
 Brown adipocytes	'Multi-locular' fat droplets; high mitochondrial content; $UCP1^+$	Adaptive thermogenesis Regulation of nutrient homeostasis	Organized as distinct depots in interscapular, axillary, and peri-renal regions	Interscapular region in infants; cervical, supraclavicular, axillary, and paravertebral regions in adults	$Myf5^+/Pax7^+$ dermomyotomal precursors
 Beige adipocytes	'Multi-locular' fat droplets; high mitochondrial content; $UCP1^+$ upon activation	Adaptive thermogenesis Regulation of nutrient homeostasis	Induced and interspersed within white adipose tissue More abundant in inguinal WAT than gonadal WAT	Interspersed among brown and white adipocytes in cervical, supraclavicular, axillary, and paravertebral regions in adult	Smooth muscle-like origin in adults

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Figure 1. Properties of adipose tissue in rodents and humans.

recruitment in rodents. An exercise-induced muscle-derived hormone, meteorn-like, activates this cascade to stimulate 'browning' of WAT. Many other hormones and secreted factors promote beige adipocyte formation in WAT, including the myokines irisin and β-aminoisobutyric acid, the cardiac peptides ANP, BNP, and cardiotropin-1, as well as bile acids, fibroblast growth factor 21 (FGF21), and vascular endothelial growth factor A (VEGFA).

Anatomically distinct adipose depots

White adipocytes can appear throughout the body but are mostly organized into distinct tissues, or 'depots'. The major white adipose depots can be divided on the basis of their anatomical location — visceral or subcutaneous. The importance of these anatomically distinct depots has been demonstrated by clinical studies that strongly indicate a correlation between adipose tissue distribution (rather than simply overall mass) and risk for metabolic and cardiovascular disease. Those individuals who preferentially accumulate adiposity in the visceral/abdominal region are more prone to developing insulin resistance, cardiomyopathy, and certain cancers when compared with equally obese individuals whose adiposity is distributed to more subcutaneous regions (e.g. arms, legs, and buttocks). In fact, subcutaneous adiposity appears to provide a protection against metabolic disease. It should be noted that, in the complete absence of adipose tissue (i.e. lipodystrophy), insulin resistance and other chronic disorders ensue. This has led to a notion that perhaps there is 'good' white fat and 'bad' white fat.

The mechanisms linking visceral adiposity to metabolic disease are of great interest given the rising epidemic of obesity. Certainly part of the explanation could be related to anatomical location and blood flow; visceral adipocytes lie in closer proximity to key tissues of nutrient homeostasis (e.g. gut, liver, and pancreas). Transplantation studies, however, suggest an alternative or parallel explanation. Transplantation of visceral adipose tissue into subcutaneous regions still leads to metabolic dysfunction. This suggests that the maladaptive properties of visceral WAT are at least in part depot-intrinsic. The key question is whether differences between the depots are due to the cellularity of the tissue (smaller healthier adipocytes vs. hypertrophic fat cells), presence of non-parenchymal cell types (e.g. pro-inflammatory macrophages), or intrinsic differences at the level of the fat cell itself. The latter hypothesis is supported by a number of recent observations showing that anatomically distinct adipocytes arise from distinct developmental origins, and that anatomically distinct adipocytes have vastly different gene expression programs. The precise functional differences between subcutaneous white adipocytes and visceral white adipocytes remain

largely unexplored. However, the current thinking is that multiple types of energy-storing white adipocytes may exist, just as there are multiple types of thermogenic fat cells.

Another important question is how body fat distribution is controlled. Preferential expansion of subcutaneous adipose tissue in the legs and buttocks is more frequently observed in females ('pear shape' obesity). The 'apple shape' or visceral adiposity is prominent amongst males. Sex hormones, particularly estrogen, appear to play a key role in this process. Understanding how adipose tissue distribution is regulated may lead to novel therapeutic treatments for chronic disease (Figure 2).

Lastly, it is worth noting that adipocytes exist outside of the major depots and accumulate ectopically within the parenchymal population of other tissues and organs. Adipocytes can accumulate in the skeletal muscle, particularly following muscle injury. Likewise, adipocytes exist in the bone marrow and accumulate with age. Less is known regarding the function and properties of these adipocytes. However, bone marrow adipocytes, in particular, are not inert; these cells produce adiponectin at levels significant enough to exert systemic effects. Understanding the precise properties of these lesser-studied adipocyte populations may help elucidate additional functions of fat cells in physiology and homeostasis.

Adipose development

Transcriptional control of adipocyte differentiation

A vast majority of the current knowledge of adipocyte development is derived from cellular studies of adipocyte differentiation. Since the 1970s, fat cell differentiation, or 'adipogenesis', of immortalized fibroblast cell lines has been an extensively studied model of cellular differentiation. Of the available cell lines, the 3T3-L1 pre-adipocyte cell line remains the most widely used cellular model system. 3T3-L1 cells are highly committed to the adipose lineage. Treatment of confluent cultures with a hormonal/pharmacological cocktail consisting of dexamethasone, iso-butyl-methyl-xanthine, and insulin (generally referred to as 'DMI medium') results in efficient differentiation into white adipocytes. Importantly, these *in vitro* derived cells largely, but not entirely, resemble *bona fide* adipocytes found *in vivo*.

Perhaps the most important information to emanate from these cellular studies is the vast network of transcription factors that coordinate the differentiation and maintenance of the adipocyte fate. Numerous transcriptional components that are involved in adipogenesis have been described. However, at the center of the network is the nuclear hormone receptor peroxisome proliferator activated receptor γ (PPARγ), which is widely accepted as the 'master regulator' of adipogenesis. Its expression is low in adipose precursors but is dramatically upregulated during adipogenesis. Once activated, PPARγ participates in very powerful positive feedback loops, creating a 'snowball effect' that enhances commitment to the adipocyte fate. PPARγ directly activates its own expression and also activates the expression of its upstream regulator, CCAAT/enhancer binding protein α (C/EBPα), or transcriptional partners, such as the Groucho/Grg/TLE family member TLE3. Importantly, PPARγ is sufficient to drive the full adipogenic program in mesenchymal cells and is absolutely essential for adipocyte formation in rodents and humans.

The factors described above represent a 'core' transcriptional program that guides the terminal differentiation of adipocytes, white or brown. Tremendous effort is now placed on identifying the transcriptional mechanisms guiding the formation of depot-specific adipocytes. Progress has been made in identifying key brown and beige adipocyte determination factors. Expression of transcription factors, such as EBF2, PRDM16, and PPAR-γ coactivator 1α (PGC-1α), is enriched in brown and beige adipocytes compared with white adipocytes and functions to regulate the thermogenic program of these fat cells. Most recently, the transcription factor interferon regulatory factor 4 (IRF4) has been implicated in thermogenic gene regulation in adipocytes, serving as the key transcriptional partner of PGC-1α. On the other hand, TLE3 is selectively expressed in white adipocytes and antagonizes the thermogenic gene program and promotes lipid storage. Less is known about the transcriptional mechanisms that determine a subcutaneous or visceral white adipocyte cell fate; however, recent studies have identified forkhead box protein A3 (Foxa3), Wilm's tumor 1 (WT1), and short stature homeobox 2 (Shox2) as depot-selective regulators of adipogenesis or adipocyte function, with Foxa3 and WT1 having gonad-specific roles and Shox2 an inguinal-specific role.

The 3T3-L1 and primary pre-adipocyte cell lines have been instrumental in defining the transcriptional network that controls the terminal differentiation into adipocytes. In recent years, emphasis has been placed on elucidating the early transcriptional events that control the initial commitment of pre-adipocytes to the adipose lineage. The multi-C_2H_2 zinc-finger protein Zfp423 is one transcriptional determinant of preadipocyte commitment. Zfp423 induces adipose lineage commitment, at least in part, by regulating preadipocyte levels of PPARγ. Zfp423 expression during adipogenesis is repressed by the highly related factor Zfp521, which acts as a repressor of adipogenesis while promoting osteoblast differentiation. Zfp521 exerts this function through interaction with EBF1, another transcription factor required for early adipose commitment. Tcf7l1 also serves as an important regulator of adipogenic lineage commitment: this transcriptional repressor regulates the expression of cytostructural genes and coordinates cell shape or cell–cell contact with the activation of adipogenesis.

The cellular models of adipogenesis have provided great insight into the cellular and transcriptional machinery controlling adipocyte differentiation. One big challenge going forward is to determine the relative importance of these factors *in vivo*, within specific fat depots. Adipogenesis occurs at both the embryonic stage and in adult animals under different contexts (e.g. obesity, cold exposure, and injury). Whether there are temporal requirements for the identified adipogenic factors remains unclear. Excellent tools are now available for Cre–loxP-mediated gene targeting in terminally differentiated adipocytes in mice. One example is the adiponectin–Cre transgenic mouse line, which expresses Cre recombinase under the control of the adiponectin gene

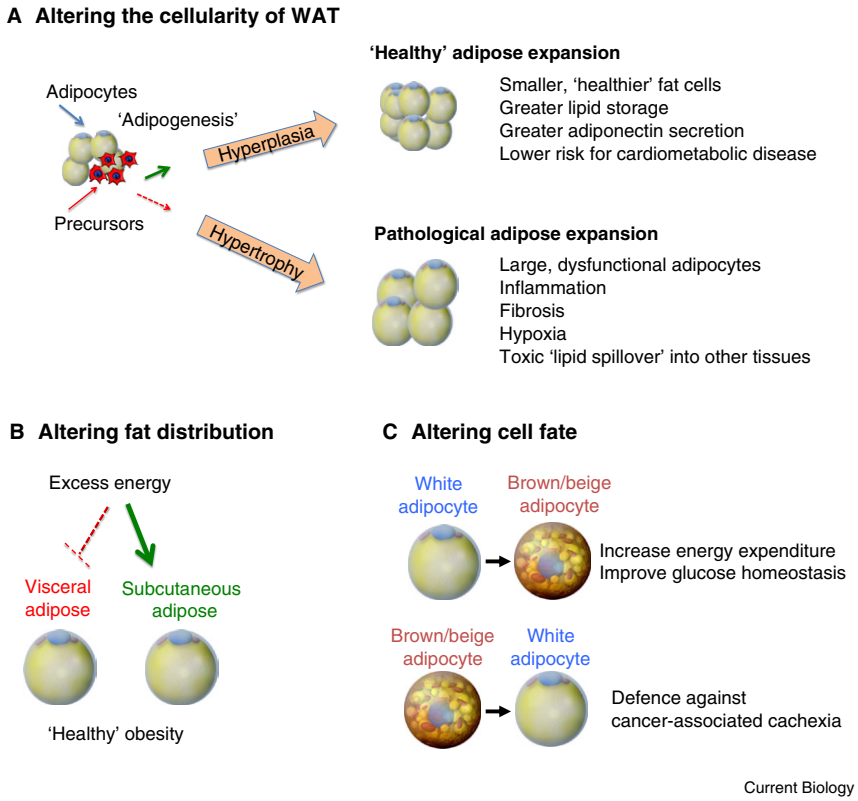

Figure 2. Manipulating adipose development to combat chronic disease.
(A) Increasing the number of fat cells, rather than the size of fat cells, in the face of positive energy balance may lead to healthier adipose tissue in the obese setting. (B) Likewise, directing excessive energy towards subcutaneous adipose, rather than visceral regions, may help improve metabolic health in the setting of obesity and lower the risk for cardiometabolic disease and cancer. (C) Direct reprogramming of white preadipocytes/adipocytes into energy-burning brown/beige adipocytes may be an effective treatment for weight loss or insulin resistance in the setting of obesity. Inhibiting the formation of thermogenic adipocytes or converting them to white adipocytes may help combat cancer cachexia.

promoter. However, specific Cre lines that target adipose precursors are still needed. Furthermore, genetic models that allow depot-specific WAT targeting are also required. It is likely that these tools will eventually evolve from a better understanding of the molecular properties of adipose precursor cells and the ontogeny of fat cells *in vivo*.

Sorting out the adipose lineage

Most have long believed that all adipose depots are mesenchymal in origin, and closely related in lineage. However, in recent years, modern Cre–loxP-mediated lineage-tracing approaches have shed light on the complexity of adipose development. It is now clear that anatomically distinct brown and white adipose depots arise from vastly distinct precursor populations, and at different times. In mice, craniofacial WAT, but not peripheral fat depots, is derived from a neural crest lineage. Gonadal and mesenteric WAT, but not subcutaneous depots, descend from WT1-expressing mesothelium. Brown adipocytes, but not most white adipocytes, descend from a Myf5$^+$/Pax7$^+$ skeletal-muscle-like lineage. Interestingly, most beige adipocytes do not arise from a Myf5$^+$/Pax7$^+$ lineage; these cells share characteristics with and descend from a smooth-muscle-like lineage. Temporally, inguinal white adipocytes and classical brown adipocytes develop almost entirely during embryogenesis, with lipid filling occurring postnatally. Gonadal and other visceral WAT develops postnatally. It should be noted that many assume that individual WAT depots arise from a singular source. Further analyses of Myf5 and Pax3 lineage-tracing experiments suggest a significant heterogeneity in the developmental origin of anatomically distinct fat depots; many WAT depots contain both Myf5$^+$/Pax3$^+$ and Myf5$^-$/Pax3$^-$ adipocytes. Additional studies will be required to determine whether these distinct populations of adipocytes within individual fat depots are actually functionally distinct.

A significant barrier to advancing our understanding of adipose development is the lack of genetic tools suitable to identify, isolate, and manipulate distinct adipose precursor cell populations *in vivo*. In recent years, a number of approaches have been used to tackle this problem. Most notably, a number of laboratories have successfully combined fluorescence-activated cell sorting analysis with candidate stem cell markers to reveal hierarchical populations of highly adipogenic adipose precursor cells. Adipogenic cells are of non-endothelial and non-hematopoietic origin (CD31$^-$ CD45$^-$) and express stem/surface cell markers, such as Sca1, CD34, CD29, and platelet-derived growth factor α (PDGFRα). A more primitive 'stem cell' subpopulation can be identified from this pool on the basis of CD24 expression. Importantly, lineage-tracing approaches reveal that adipocytes descend from cells that express PDGFRα at some stage during their genesis; this includes adipocytes formed during development as well as new fat cells formed in adult animals. However, it is not clear whether the adipose precursor cells found in adult WAT are identical to those found in the embryo. Other approaches utilize transgenic reporter strains in which the expression of fluorescent proteins is driven by the locus of key regulators of adipose lineage commitment (e.g. PPARγ, Zfp423, and pre-acdipocyte factor 1 (Pref-1)). The combined use of many of these new reagents should allow for the identification of hierarchical populations of adipose precursor cells and provide insight into how these different cell populations are regulated spatially and temporally.

Adipose tissue remodeling and dysfunction in chronic disease

Cardiometabolic disease

Obesity confers significant risk for developing metabolic disorders; however, upwards of one-third of obese individuals are resistant to developing metabolic syndrome, at least for a period of time. This suggests that additional factors, outside of increased adiposity *per*

se, determine metabolic health in obesity. Tremendous insight into these determinants has been gained by comparing obese individuals with metabolic syndrome (Obese-MetSyn) with obese individuals who are relatively metabolically healthy (Obese-Healthy). Emerging from these studies, as well as from numerous rodent studies, is a now widely accepted model in which the manner by which WAT remodels in response to caloric excess is a critical determinant of metabolic disease. In principle, the expansion of fat mass can occur by two mechanisms: increased triglyceride storage in existing adipocytes, leading to 'adipocyte hypertrophy' (enlargement of cell size); or increased formation of new adipocytes, or 'adipocyte hyperplasia' (Figure 2).

In Obese-MetSyn individuals, WAT expands predominantly through adipocyte hypertrophy, rather than adipocyte hyperplasia. Enlarged fat cells outstrip their vascular supply and become hypoxic, leading ultimately to tissue fibrosis, inflammation, and adipocyte apoptosis. These 'overworked' fat cells reach their storage capacity; this leads to the deleterious accumulation of lipids in peripheral tissues unequipped to handle excess energy storage (termed 'lipotoxicity'). Moreover, these adipocytes become dysfunctional; they fail to produce protective adipokines, such as adiponectin, and overproduce pro-inflammatory cytokines that can trigger systemic inflammation, cardiac dysfunction, and insulin resistance. However, in Obese-Healthy individuals WAT expansion through the recruitment of new fat cells leads to adequate storage of excess triglyceride over numerous adipocytes; this limits the stress put on individual fat cells and preserves their function, delaying adipose inflammation, fibrosis, and ectopic lipid deposition. In this model, metabolic syndrome in obesity is related to a relative deficiency of functional adipocytes, despite the elevated adiposity. In accordance with this model, the metabolic sequelae of obesity are actually similar to those observed in lipodystrophic individuals who completely, or almost completely, lack adipocytes altogether. In this regard, healthy adipocytes are *protective* against metabolic disease and cardiac dysfunction, serving as a 'lipid sink' for excess energy.

Cancer

There is a growing body of evidence from both clinical and preclinical studies that indicates that increased adiposity is associated with elevated incidence, morbidity and mortality of numerous cancer subtypes. While there is tremendous interest in understanding how obesity links to cancer progression at the molecular level, the precise mechanisms remain unclear. In principle, the effects on tumor growth or metastasis in obesity can be secondary to the metabolic sequelae, including elevated insulin/insulin-like growth factor (IGF) signaling or hyperglycemia. However, intriguing data point also to the adipose tissue itself as a direct regulator of tumor growth. The adipose tissue microenvironment, including vascular-associated stromal cells and various immune cell populations, may influence tumor cells. For instance, rodent models of liver and colon cancer indicate that obesity-related chronic inflammation, mediated by IL-6 and TNF-α, contribute to tumor initiation and progression. Clinical studies as well as cellular analyses have implicated adipokines, such as leptin and adiponectin, in ovarian, breast, colon, and other types of cancer. Additional studies of how adipocyte-derived products regulate tumor cell biology will be essential to unveil the precise links between adipose tissue in obesity and cancer.

It should be noted that the conversation between adipose tissue and tumor cells is not one-sided; tumors can have a tremendous impact on adipose tissue function. In particular, many cancer patients suffer from cachexia, a debilitating condition characterized by the significant loss of muscle and fat mass due to increased energy expenditure. In rodents and humans, cachexia is associated with 'browning' of the adipose tissue. The induction of the thermogenic program in fat is required for the cachectic effects of tumors and appears to be mediated, at least in part, by tumor-derived parathyroid-hormone-related protein signaling. This new insight now suggests a viable strategy to combat cancer cachexia and improve patient survival. Moreover, a deeper understanding of how the beige fat program can develop in this context may lead to new strategies both to enhance the thermogenic function of fat in obesity and diabetes and to inhibit this program in cachectic individuals (Figure 2).

Conclusions

For most of the 20th century, white adipocytes were viewed as mere energy-storing cells that served as a fuel bank. It is now clear that adipocytes are quite complex and regulate many facets of energy metabolism, physiology, and disease. Moreover, it appears that multiple types of brown and white adipocytes exist, each with distinct developmental origins. This extraordinary complexity creates many great opportunities for unique therapeutic intervention. Adipokine-based therapies remain attractive for the treatment of cardiovascular disease and insulin resistance. Furthermore, our increasing knowledge of adipocyte development may inform novel strategies for manipulating the fate and function of brown and white adipocytes (Figure 2). Our view of adipocytes has changed entirely over the past twenty years alone. It is almost certain that many more surprises are in store for the future.

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Touchstone Diabetes Center, Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Blvd. K5.240, Dallas, TX 75390-8549, USA.
E-mail: Rana.Gupta@UTSouthwestern.edu